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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,625	07/28/2000	GEORGII GEORGIEV	0652.1630001	5330

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EXAMINER

RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 12/04/2002

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/462,625

Applicant(s)

GEORGIEV ET AL.

Examiner

Stephen L. Rawlings, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendment filed June 14, 2002 in Paper No. 14 is acknowledged and has been entered. Claims 1-52 have been canceled. Claims 53-93 have been added.
2. Claims 53-93 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

3. Unless specifically reiterated below, the grounds of claim rejections set forth in the previous Office action mailed March 14, 2002 (Paper No. 13) have been withdrawn.

Grounds of Claim Rejections Maintained and Reply to Applicants' Remarks

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
5. Claims 53-55, 57-63, 65, 66, 68, 71, and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *making* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 2 from positions 1 or 20 to position 182, wherein said polypeptide could generate an antibody that specifically binds to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 2, and the polypeptide that is encoded by said nucleic acid molecule, does not reasonably provide enablement for *making* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is less than 100% identical to the amino acid sequence set forth in SEQ ID NO: 2 from positions 1 or 20 to position 182, wherein said

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polypeptide mediates apoptosis or inhibits tumor growth, or any polypeptide encoded by said nucleic acid molecule.

Claims 64 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *making* a synthetic nucleic acid molecule comprising a polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2, a non-naturally occurring nucleic acid molecule comprising the polynucleotide sequence that encodes SEQ ID NO: 2, and a polypeptide that consists essentially of the amino acid sequence set forth in SEQ ID NO: 2 from position 145 to 160, does not reasonably provide enablement for *making* any isolated naturally occurring nucleic acid molecule comprising a polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2 or any polypeptide comprising amino acids 145 to 160 of SEQ ID NO: 2.

Claims 73, 76-83, 86-88, and 90-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *making* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4, wherein said polypeptide could generate an antibody that specifically binds to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4, and the polypeptide that is encoded by said nucleic acid molecule, does not reasonably provide enablement for *making* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is less than 100% identical to the amino acid sequence set forth in SEQ ID NO: 4, wherein said polypeptide mediates apoptosis or inhibits tumor growth, or a polypeptide that is encoded by said nucleic acid molecule.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** the invention commensurate in scope with these claims.

The specification teaches the predicted structures of regions of the amino acid sequence set forth in SEQ ID NO: 2. The specification teaches which regions of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 are predicted to be relatively more or less antigenic. Therefore, given the benefit of

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Applicants' disclosure, one skilled in the art would have a reasonable expectation of producing without the need to perform undue experimentation, a polypeptide comprising an amino acid sequence that could be used to generate an antibody that binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. Even though the specification does not teach the regions of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4 that are predicted to be more or less antigenic, one skilled in the art would nevertheless have a reasonable expectation of successfully *producing* a polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4, which could be used to generate an antibody that binds to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4.

Additionally, the specification teaches that cells exposed to conditioned supernatants of cultures of tumor cells expressing a nucleic acid molecule encoding the polypeptide of SEQ ID NO: 2 are induced to undergo apoptosis. The specification teaches that a neutralizing antibody that binds the polypeptide of SEQ ID NO: 2 abolishes this effect, which suggests that the presence of the polypeptide of SEQ ID NO: 2 in the conditioned supernatants accounts for the effect. Furthermore, the specification teaches that tumor cells expressing a nucleic acid molecule encoding the polypeptide of SEQ ID NO: 2 grow more slowly than tumor cells that do not express the nucleic acid molecule. Therefore, given the benefit of Applicants' disclosure, one skilled in the art would have a reasonable expectation of *producing* without the need to perform undue experimentation, a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 that induces apoptosis or inhibits tumor growth.

However, the teachings of the specification cannot be extrapolated to the enablement of the claims because the specification does not teach one to **make** any nucleic acid molecule other than one that encodes a protein having the amino acid sequence set forth in SEQ ID NO: 2, which mediates apoptosis or inhibits tumor growth. While the specification teaches that a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 can induce apoptosis or inhibit tumor growth, the specification does not teach how any other nucleic acid

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molecule can be produced that encodes a polypeptide that comprises an amino acid sequence that is not identical to the amino acid sequence set forth in SEQ ID NO: 2, which is able to mediate apoptosis or inhibit tumor growth. Moreover, the specification does not teach which amino acid residues of SEQ ID NO: 2 must be conserved, or which amino acids can be replaced, and by which other amino acids, within SEQ ID NO: 2 so that a protein comprising a variation of SEQ ID NO: 2 would also be capable of inducing cells to undergo apoptosis, or of slowing the growth rate of tumor cells. Therefore, because of the high level of unpredictability in the art, as established in the previous Office action, one skilled in the art would not have a reasonable expectation of successfully producing any other species of the claimed genus of nucleic acid molecules, with the exception of the one comprising the polynucleotide sequence set forth in SEQ ID NO: 1, without the need to perform additional, undue experimentation.

Furthermore, the specification does not exemplify the production of a polypeptide comprising only amino acids 20 to 182 of SEQ ID NO: 2 or amino acids 1 to 191 of SEQ ID NO: 4 that has been shown to mediate apoptosis or inhibit tumor growth. While it is plausible that a polypeptide comprising only the fragment of SEQ ID NO: 2 spanning positions 20 and 182 might have an activity of a polypeptide comprising the full length amino acid sequence set forth in SEQ ID NO: 2, given the high level of unpredictability in the art, one skilled in the art would not have a reasonable expectation of successfully producing a polypeptide comprising amino acids 20 to 182 of SEQ ID NO: 2 that is capable of inducing apoptosis or inhibiting tumor growth without having to first perform additional, undue experimentation. As SEQ ID NO: 4 is only marginally similar to SEQ ID NO: 2, one skilled in the art would not have a reasonable expectation of successfully producing a polypeptide comprising amino acids 1 to 191 of SEQ ID NO: 4 that is capable of inducing apoptosis or inhibiting tumor growth without having to first perform additional, undue experimentation.

Skolnick, et al (*Trends in Biotechnology* 18: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based*

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approaches to function prediction). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that the polypeptide of SEQ ID NO: 4 is capable of inducing apoptosis or inhibiting tumor growth. Therefore, given Applicants' disclosure, while a skilled artisan can make a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4, the skilled artisan would not have a reasonable expectation of making a nucleic acid molecule encoding such a polypeptide that mediates apoptosis or inhibits tumor growth without need of performing additional, undue experimentation.

With particular regard to claim 57, although the amino acid sequence set forth in SEQ ID NO: 1 encodes a murine, more specifically a mouse protein, the specification does not teach one to make any other nucleic acid molecule that encodes a murine protein. For example, the specification does not teach one to make a nucleic acid molecule that encodes a rat protein, or another mouse protein that comprises an amino acid sequence that is not identical to the amino acid sequence set forth in SEQ ID NO: 2. By the same token, with particular regard to claim 78, although the amino acid sequence set forth in SEQ ID NO: 3 encodes a human protein, the specification does not teach one to make any other nucleic acid molecule that encodes a human protein. Thus, the teachings of the specification are not reasonable commensurate in scope with the claims. Because the structure of a murine or human protein cannot be predicted, even given knowledge of Applicants' instant disclosure of SEQ ID NO: 2 and SEQ ID NO: 4, the structure of a nucleic acid molecule encoding a murine protein cannot be predicted. Therefore, one could not make any nucleic acid molecule encoding a murine protein other than the one that comprises the polynucleotide sequence set forth in SEQ ID NO: 1 or a fragment thereof with a reasonable expectation of success.

With particular regard to claims 64 and 93, given the benefit of Applicants' disclosure, one could produce a synthetic nucleic acid molecule comprising a

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polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2, including, of course, a synthetic nucleic acid molecule that comprises a polynucleotide sequence encoding a polypeptide that comprises the entire amino acid sequence, or any portion thereof, set forth in SEQ ID NO: 2. Furthermore, one could isolate a naturally occurring nucleic acid molecule that comprises the polynucleotide sequence set forth in SEQ ID NO: 1, which encodes the amino acid sequence set forth in SEQ ID NO: 2. However, one could not produce any other naturally occurring nucleic acid molecule that comprises a polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2 with a reasonable expectation of success without the need to first perform additional, undue experimentation. For example, given only benefit of Applicants' disclosure, one could not produce the gene or any allele thereof that comprise a polynucleotide sequence that encodes a protein having the amino acid sequence set forth in SEQ ID NO: 2 or any variant thereof. As a further example, a large number of nucleic acid molecules may encode a polypeptide comprising amino acids 145 to 160 of SEQ ID NO: 2; none, or few of which will bear any structural relationship to the polypeptide of SEQ ID NO: 2, beyond of course having an amino acid sequence that shares the fifteen amino acid sequence set forth in SEQ ID NO: 2 between positions 145 and 160. Thus, again, the teachings of the specification are not reasonably commensurate in scope with the claims; and given the inability to predict the protein structures, the skilled artisan could not produce even a substantial number of species of the claimed genus of nucleic acid molecules encoding a polypeptide comprising amino acids 145 to 160 of SEQ ID NO: 2.

It is noted that Applicants have traversed these grounds of rejection in Paper No. 14 arguing that the specification provides an enabling disclosure for making the claimed invention, since the specification discloses predicted antigenic regions of the polypeptide of SEQ ID NO: 2 that can be used to raise antibodies that bind the polypeptide. In addition, Applicants have noted that Figure 2 depicts the predicted structures of various regions of the polypeptide of SEQ ID NO: 2 and assert that the specification, therefore, provides sufficient guidance to enable the skilled artisan to

make polypeptides that have amino acid sequences differing from the amino acid sequence set forth in SEQ ID NO: 2.

Applicants' arguments have been carefully considered, but in view of the preponderance of evidence have not been found persuasive. One skilled in the art would not base decisions regarding which amino acid substitutions may or may not be tolerated within the amino acid sequence of SEQ ID NO: 2 upon knowledge of the predicted antigenicity of a particular region of the protein of SEQ ID NO: 2. A correlation between the predicted structure and the function of the claimed polypeptides to induce apoptosis or inhibit tumor growth is not evident, nor has it been disclosed. Therefore, given only benefit of Applicants' disclosure, the skilled artisan would not know which amino acids or regions of the amino acid sequence of SEQ ID NO: 2 are essential, or non-essential.

Although Applicants have argued that proteins are "surprisingly tolerant of amino acid substitutions" (page 16, paragraph 2), the art lacks predictability. For example, as noted in the previous Office action, Lazar, et al teach that even a *single conservative* amino acid substitution can unexpectedly affect the activity of a protein. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predicting which changes can or cannot will be tolerated in a polypeptide's amino acid sequence without disrupting its function would require a thorough knowledge of, and direction and guidance with regard to which positions in the polypeptide's sequence, if any *are tolerant* of substitution. Moreover, determining which amino acid substitutions can or cannot be made requires detailed knowledge of which regions of a polypeptide are conserved or not conserved, essential or not essential, and how the structure of a polypeptide relates to its function. Utilizing predicted structural determinations of particular regions of a protein in the absence of such direction and guidance to ascertain functional aspects of the claimed polypeptides and finally to determine what changes will be tolerated is complex and well outside the realm of routine experimentation, but the suggestion that the predicted antigenicity of particular regions of a protein can be utilized to determine functional domains of a protein is unfounded.

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In addition, Applicants have argued that because the specification teaches methods, which are exemplified in Examples 5 and 6, that would enable the skilled artisan to determine which variants of SEQ ID NO: 2 are able to induce apoptosis or inhibit tumor growth. In reply, it is appropriately noted that the claims are not limited to nucleic acid molecule encoding a polypeptide that induces apoptosis or inhibits tumor growth, since alternatively, the polypeptide is merely required to be capable of generating an antibody that binds to the polypeptide of SEQ ID NO: 2. Nevertheless, as Applicants are apparently aware, as the specification does not teach how nucleic acid molecules that encode polypeptides that are less than 100% identical to SEQ ID NO: 2 *that induce apoptosis or inhibit tumor growth* can be made, the artisan would be left to manufacture each and every species of nucleic acid molecule encoding a polypeptide having an amino acid sequence varying from the amino acid sequence set forth in SEQ ID NO: 2 by at most 5% and then determine whether the protein induces apoptosis or inhibits tumor growth. Even allowing only one amino acid in a sequence the length of SEQ ID NO: 2, i.e., 182 amino acids, to vary, and limiting the variation to a deletion, insertion, or replacement, and limiting the pool of amino acids with which to make the insertion or replacement to those that are naturally occurring, the claims would encompass a genus of roughly 7,300 members; but the present claims allow for a substitution, insertion, or deletion at any number of positions up to about nine to be made within the amino acid sequence of SEQ ID NO: 2, so the present claims may encompass a still vast genus of polypeptides. Because one would reasonably imagine that the claims encompass many non-working embodiments, which could not be identified by any means other than producing a species of polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 2 and determining whether or not the species induces apoptosis or inhibits tumor growth, finding the working embodiments among the possibilities would require undue experimentation.

6. Claims 53-56, 59-63, 65, 66, and 68-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *using* a nucleic acid

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molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is identical to the amino acid sequence set forth in SEQ ID NO: 2 from positions 1 to position 182, wherein said polypeptide mediates apoptosis or inhibits tumor growth, does not reasonably provide enablement for *using* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is less than 100% identical to the amino acid sequence set forth in SEQ ID NO: 2 from positions 1 to position 182 or at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 2 from positions 20 to 182, wherein said polypeptide could generate an antibody that specifically binds to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 2.

Claims 64 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *using* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide consisting essentially of amino acids 145 to 160 of SEQ ID NO: 2 or a polypeptide that comprises the amino acid sequence set forth in SEQ ID NO: 2 and a polypeptide consisting essentially of amino acids 145 to 160 of SEQ ID NO: 2 or comprising the amino acid set forth in SEQ ID NO: 2, does not reasonably provide enablement for *using* a nucleic acid molecule comprising a polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2.

Claims 73, 76-83, 86-88, and 90-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *using* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4, wherein said polypeptide could generate an antibody that specifically binds to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4, does not reasonably provide enablement for *using* a nucleic acid molecule comprising a polynucleotide sequence that encodes a polypeptide having a first amino acid sequence that is less than 100% identical to the amino acid sequence set forth in SEQ ID NO: 4, wherein said polypeptide mediates apoptosis or inhibits tumor growth.

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The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims.

The specification teaches that a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2 can be used to generate an antibody that binds specifically to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, induce apoptosis, or inhibit tumor growth. It is reasonable to expect that a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 could also be used to generate an antibody that binds specifically to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, induce apoptosis, or inhibit tumor growth. Additionally, the specification teaches that a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2 that spans positions 145 and 160 can be used to produce an antibody that binds specifically to the polypeptide of SEQ ID NO: 2. It is reasonable to expect that a substantial number of members of a genus of polypeptides consisting essentially of the amino acid sequence set forth in SEQ ID NO: 2 that spans positions 145 and 160 could also be used to produce an antibody that binds specifically to the polypeptide of SEQ ID NO: 2.

However, given only the teachings of the specification, considering the state of the art and the unpredictability associated with the art, it would not be reasonable to expect that any polypeptide that comprises an amino acid sequence that is less than 100% identical to the amino acid sequence set forth in SEQ ID NO: 2 could be used to induce apoptosis, or inhibit tumor growth. While it might be reasonable to expect that any such variant of SEQ ID NO: 2 might be used to generate an antibody that binds to a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 2, unless the polypeptide can be used to induce apoptosis or inhibit tumor growth, it is apparent that the specification fails to teach how such variants can be used.

As claims 64 and 93, in particular, merely require a polypeptide to comprise an amino acid sequence that comprises amino acids 145 to 160 of SEQ ID NO: 2, it is apparent that a substantial number of members of the claimed genus of nucleic acid molecules and proteins will not bear any remarkable structural or functional homology to

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the polypeptide of SEQ ID NO: 2. The specification, however, only teaches one to use the polypeptide consisting essentially of the amino acid sequence set forth in SEQ ID NO: 2; and therefore the teachings of the specification are not reasonably commensurate in scope with the claims.

With regard to claims 73-92, as noted in the rejection above, the specification does not exemplify the use of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 4 to induce apoptosis or inhibit tumor growth. For the reasons set forth above, it would be unreasonable to expect that the polypeptide of SEQ ID NO: 4 or any of the claimed variants thereof could be used to induce apoptosis or inhibit tumor growth. Although it is reasonable to expect that at least a substantial number of the claimed polypeptides could be used to generate antibodies that specifically bind to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4, unless the polypeptides can be used to induce apoptosis or inhibit tumor growth, it is apparent that the specification fails to teach one to use the claimed polypeptides.

Regarding Applicants' remarks, which were made of record in Paper No. 14, it appears that Applicants are aware that one skilled in the art could not use at least a substantial number of members of the claimed genus of nucleic acid molecules and polypeptides without having the need to first determine which polypeptides having amino acid sequences varying from that set forth in SEQ ID NO: 2 induce apoptosis or inhibit tumor growth. Therefore, with the exception of a polypeptide comprising essentially the amino acid sequence set forth in SEQ ID NO: 2, one skilled in the art could not use members of the claimed genus of nucleic acid molecules and polypeptide without need to perform undue experimentation.

7. Claims 53-56, 59-67, 68, 70, 73, 75, 78-83, 85, 88, and 89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action mailed March 14, 2002 (Paper No. 13).

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Applicants have traversed these grounds of rejection in Paper No. 14. Applicants' arguments have been carefully considered but not found entirely persuasive. Although the claims recite limitations requiring the members of the claimed genus of polypeptides encoded by the claimed genus of nucleic acid molecules to be at least 95% identical to a reference amino acid sequence and to have the ability to either (a) generate an antibody that binds specifically to a protein consisting of said reference amino acid sequence, (b) induce apoptosis, or (c) inhibit tumor growth, if the members of the claimed genus of polypeptides do not induce apoptosis or inhibit tumor growth, but merely generate an antibody that binds specifically to a polypeptide consisting of said reference amino acid sequence, the written description would not reasonably convey to the skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, or meet the requirements set forth under 35 USC § 112, first paragraph. This is because given only the benefit of the disclosure, one skilled in the art could not envision or recognize that which is claimed from that which is not, or distinguish the members of the claimed genus from others using a functional assay, because any protein that comprises an amino acid sequence that is at least 95% identical to a reference amino acid sequence would be expected to be capable of generating an antibody that binds specifically to a polypeptide consisting of the reference amino acid sequence. Moreover, the recitation of a limitation requiring the members of the claimed genus of polypeptides to generate an antibody that binds specifically to a protein consisting of a reference amino acid sequence, would not convey with reasonable clarity to those skilled in the art that, as of the filing date sought, that he or she was in possession of the invention, because the recitation of limitation does not provide a description of any uniquely defining or identifying feature that is common to at least a substantial number of members of the claimed genus, which would descriptively set the genus apart from just any polypeptide having the required similarity to the reference amino acid sequence.

In addition, it is noted that claim 64 encompasses genomic polynucleotide sequences, or *genes*, and allelic variants thereof, which encode amino acids 145 to 160 of SEQ ID NO: 2. However, there is no evidence of record that Applicants had in their

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possession such embodiments of the claim at the time the application was filed. Furthermore, recitation of the limitation requiring the members of the claimed genus of nucleic acid molecules to encode a polypeptide having an amino acid sequence comprising amino acids 145 to 160 is not sufficiently descriptive of at least a substantial number of members of the claimed genus. Claim 64 encompasses a broad genus of nucleic acid molecules with widely varying attributes, but the specification only describes the detailed structure of one species, namely the polypeptide consisting of SEQ ID NO: 2. The *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement* make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, the requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001; see especially page 1106, column 3). If there is substantial variation among the members of the genus, one must describe a sufficient variety of species to reflect the variation within the genus; therefore SEQ ID NO: 2 is not representative and its mere description is insufficient to meet the requirement set forth under 35 USC § 112, first paragraph. Because a correlation between the recited structural requirement and any particular function is not apparent, as members of the claimed genus of polypeptides may be envisioned that have amino acid sequences, which while comprising the amino acids 145 to 160 of SEQ ID NO: 2, will not generate antibodies that bind specifically to a protein consisting of SEQ ID NO: 2, or induce apoptosis, or inhibit tumor growth, amino acids 145 to 160 of SEQ ID NO: 2 cannot be regarded as a uniquely defining or identifying feature of at least a substantial number of members of the claimed genus, which can be used to instantly recognize the members, or to distinguish members of the genus from others that are not. In fact, the disclosure suggests that a polypeptide must minimally comprise the amino acid sequence set forth in SEQ ID NO: 2 to be regarded a member of the genus of

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polypeptides that is able to induce apoptosis or inhibit tumor growth; and for the reasons stated above, describing members of the claimed genus as capable of generating an antibody that binds to a protein consisting of SEQ ID NO: 2 would not reasonably convey to the skilled artisan that Applicants had possession of the invention at the time the application was filed, because it would not be unexpected that each and every polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 would be capable of doing so, and recitation of this latter requirement is not expected to be substantially limiting.

Finally, regarding claims 59 and 78, the specification does not disclose any uniquely defining or identifying feature that is common among at least a substantial number of members of the claimed genera of nucleic acid molecules encoding murine and human polypeptides. Although the specification teaches that SEQ ID NO: 2 is the amino acid sequence of a mouse protein, and SEQ ID NO: 4 is the amino acid sequence of a human protein, given only benefit of the instant disclosure, one would not recognize that Applicant had possession of the invention at the time the application was filed because SEQ ID NO: 2 and SEQ ID NO: 4 do not reflect the variation in the genera, or represent a substantial number of members of the genera, because the specification fails to teach what particular structural features of SEQ ID NO: 2 or SEQ ID NO: 4 are common among at least a substantial number of members of the genera. For example, given two nucleic acid molecules, one isolated from a mouse and another isolated from a human, both of which are at least 95% identical to a reference sequence, one skilled in the art could not distinguish one from the other, unless provided with knowledge of a distinguishing feature.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 53-72 and 93 are given benefit of the filing date of the earliest filed application to which this application claims benefit, i.e., US Application No. 08/893,764, (now US Patent No. 6,172,211-B1), which was filed July 11, 1997. However, claims 73-92 are given only the benefit of the filing date of PCT/EP98/04287, which was filed July 10, 1998, because the claims encompass subject matter that was not sufficiently supported by the disclosure of US Application No. 08/893,764 to meet the requirements of 35 USC § 112, first paragraph. US Application No. 08/893,764, now US Patent No. 6,172,211-B1, fails to provide sufficient written description and a sufficiently enabling disclosure of the specific subject matter of claims 73-92 to meet the requirement set forth under said statute, because SEQ ID NO: 3 and SEQ ID NO: 4 are not disclosed therein.

11. Claims 53-72 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Kustikova, et al (*Genetika* 32: 621-628, 1996) and Kustikova, et al (*Russian Journal of Genetics* 32: 540-546, 1996), as evidenced by pages 4 and 5 of the results of a database search using SEQ ID NO: 2 as a query (US-09-462-625-2.p2n.rge).

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Kustikova, et al teach the polynucleotide sequence of a nucleic acid molecule isolated from mouse that encodes a polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 2, which is designated TAG7. The nucleic acid molecule of Kustikova, et al comprises a polynucleotide sequence that encodes amino acids 145 to 160 of SEQ ID NO: 2. Additionally, Kustikova, et al teaches vectors that comprise the polynucleotide sequence of the nucleic acid molecule encoding the amino acid sequence of TAG7.

Regarding claim 67, although the amino acid sequence of the polypeptide encoded by the nucleic acid molecule of the prior art differs from the amino acid sequence set forth in SEQ ID NO: 2, it appears that Applicants are claiming the nucleic acid molecule that was disclosed in the prior art. On pages 18 of Paper No. 14, Applicants have stated:

Applicants are aware of the discrepancy between the sequences disclosed in the GenBank report [by Kustikova, et al] and that disclosed in the patent application. Indeed, the sequences disclosed in the instant application represent the *corrected tag 7* sequences.

Then on page 19 of Paper No. 14, Applicants have further stated:

Applicants thus submit that the discrepancy between the sequences represents a typographical error and not a variant sequence. Thus, these facts *in no way* speak to whether or not it would require undue experimentation to practice the claimed invention.

Therefore, as the polynucleotide sequence of a nucleic acid molecule is an inherent property, although the polynucleotide sequence of the nucleic acid molecule of the prior art may have been reported incorrectly, it is evident that Applicants are claiming the nucleic acid molecule that was disclosed by the prior art.

Furthermore, although the polynucleotide sequence of the nucleic acid molecule of the prior art may have been reported incorrectly, it is evident that the disclosure of the prior art is an enabling disclosure. Applicants statements regarding the teachings of the specification appear to suggest that undue experimentation would not be required to make and use the nucleic acid molecule of the prior art, despite any inaccuracy in the reported polynucleotide sequence, because as Applicants have noted in their remarks,

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the specification teaches that the artisan would have been well aware of the inherent limitations associated with sequencing nucleic acid molecules and would know, and had the means to verify the polynucleotide sequence of a nucleic acid molecule. Given the disclosure of the prior art, one of ordinary skill in the art could have produced and used the nucleic acid molecule disclosed by the prior art at the time the application was filed without benefit of Applicants' disclosure, because the prior art teaches methodology that can be used to produce and use the isolated nucleic acid molecule of the prior art; methodology that was both routine and conventional at the time the application was filed.

With regard to claim 69, although the polypeptide encoded by the nucleic acid molecule of the prior art comprises the amino acids 1 to 19 of SEQ ID NO: 2, it can be said to comprise a *first* amino acid sequence consisting of amino acids 20 to 182 of SEQ ID NO: 2.

It is noted that Applicants have traversed these grounds of rejection in Paper No. 14, arguing that the prior art does not anticipate the claimed invention. Applicants' arguments have been carefully considered but have not been found persuasive.

New Grounds of Claim Rejections

Claim Rejections - 35 USC § 112

12. Claim 93 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 93 recites the limitation "comprising amino acids 145 to 160 of SEQ ID NO:2". However, there does not appear to be proper and sufficient antecedent basis in the specification, including the original claims, for the recitation of this limitation in claim 93. Therefore, recitation of the limitation in the claim appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

This issue might be resolved if Applicants will point to particular parts of the specification that are believed to provide the necessary support. Otherwise, Applicants might amend the claims to recite the explicit language of claim 8, for example, or alternatively of lines 7-9 of page 23.

Claim Rejections - 35 USC § 102

13. Claims 73, 75-77, 79-83, and 85-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Kustikova, et al (*Genetika* **32**: 621-628, 1996) and Kustikova, et al (*Russian Journal of Genetics* **32**: 540-546, 1996).

Kustikova, et al teach the polynucleotide sequence of a nucleic acid molecule isolated from mouse that encodes a polypeptide comprising a first amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4. The nucleic acid molecule of Kustikova, et al comprises a polynucleotide sequence that is at least 95% identical to nucleotides 68 to 640 of SEQ ID NO: 3. Additionally, Kustikova, et al teaches vectors that comprise the polynucleotide sequence of the nucleic acid molecule.

Although Kustikova, et al do not teach that the polypeptide encoded by the nucleic acid molecule can be used to generate an antibody that binds specifically to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4, mediate apoptosis, or inhibit tumor growth, the nucleic acid molecule and the protein of the prior art is deemed the same as the nucleic acid molecule and the protein of the claims, absent a showing of any difference. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed nucleic acid and the protein encoded thereby. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed nucleic acid molecule and the protein encoded thereby are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

14. Claims 73, 75-77, 79-83, and 85-91 are rejected under 35 U.S.C. 102(a) as being anticipated by Selsted (WO9729765-A1).

Selsted teaches the polynucleotide sequence of a nucleic acid molecule isolated from bovine bone marrow cells that encodes a polypeptide comprising a first amino acid sequence that is at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 4. The nucleic acid molecule of Selsted comprises a polynucleotide sequence that is at least 95% identical to nucleotides 68 to 640 of SEQ ID NO: 3. The polypeptide encoded by the nucleic acid molecule of Selsted, namely the polypeptide designated BGP-A comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 4. Additionally, Selsted teaches vectors that comprise the polynucleotide sequence of the nucleic acid molecule.

Although Selsted does not teach that the polypeptide encoded by the nucleic acid molecule can be used to generate an antibody that binds specifically to a protein consisting of the amino acid sequence set forth in SEQ ID NO: 4, mediate apoptosis, or inhibit tumor growth, the nucleic acid molecule and the protein of the prior art is deemed the same as the nucleic acid molecule and the protein of the claims, absent a showing of any difference, particularly since the polypeptide encoded by the nucleic acid molecule of Selsted is more similar to the polypeptide of SEQ ID NO: 4 than the polypeptide of SEQ ID NO: 2. Again, Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed nucleic acid and the protein encoded thereby. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed nucleic acid molecule and the protein encoded thereby are different than those taught by the prior art.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

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unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

16. A timely filed terminal disclaimer in compliance with 37 CFR § 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR § 3.73(b).

17. Claims 53-64 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,172,211-B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 53-64 of this application encompass the more specific subject matter of claims 1-10 of '211.

Conclusion

18. No claims are allowed.

19. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.

Examiner

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slr

November 15, 2002

COMMUNICATIONS SECTION
NOVEMBER 15, 2002

